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Post-translational modifications of CD36 (SR-B2): Implications for regulation of myocellular fatty acid uptake

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Post-translational modifications of CD36 (SR-B2): Implications for regulation of myocellular fatty acid uptake☆

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ABSTRACT

The membrane-associated protein CD36, now officially designated as SR-B2, is present in various tissues and fulfills multiple cellular functions. In heart and muscle, CD36 is the main (long-chain) fatty acid transporter, regulating myocellular fatty acid uptake via its vesicle-mediated reversible trafficking (recycling) between intracellular membrane compartments and the cell surface. CD36 is subject to various types of post-translational modification. This review focusses on the role of these modifications in further regulation of myocellular fatty acid uptake. Glycosylation, ubiquitination and palmitoylation are involved in regulating CD36 stability, while phosphorylation at extracellular sites affect the rate of fatty acid uptake. In addition, CD36 modification by O-linked *N*-acetylglucosamine may regulate the translocation of CD36 from endosomes to the cell surface. Acetylation of CD36 has also been reported, but possible effects on CD36 expression and/or functioning have not yet been addressed. Taken together, CD36 is subject to a multitude of post-translational modifications of which their functional implications are beginning to be understood. Moreover, further investigations are needed to disclose whether these post-translational modifications play a role in altered fatty acid uptake rates seen in several pathologies of heart and muscle. This article is part of a special issue entitled: The role of post-translational protein modifications on heart and vascular metabolism edited by Jason R.B. Dyck and Jan F.C. Glatz.

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1. Introduction

CD36 (cluster of differentiation 36) is a versatile transmembrane protein. It is a member of the family of class B scavenger receptors (i.e., scavenger receptors with two transmembrane domains), which also includes scavenger receptor-B1 (SR-B1) that is involved in binding of low-density lipoprotein (LDL) and high-density lipoprotein (HDL) particles, and scavenger receptor LIMP2 (SR-B3), which functions in lysosomal protein sorting. CD36, now officially designated as scavenger receptor B2 (SR-B2) [1], is ubiquitously expressed in various tissues and binds several, mostly lipid-related ligands such as oxidized LDL particles, (long-chain) fatty acids, collagens, thrombospondin-I, apoptotic cells, and phospholipids [2]. As a result, CD36 plays a crucial role in numerous physiological processes including immune system responses, removal of apoptotic and necrotic cells, regulation of angiogenesis, and scavenging of oxidized LDL. These functions are carried out in a tissue-specific manner.

In cardiac and skeletal muscle, CD36 is the predominant protein involved in both facilitating and regulating the cellular uptake of (long-chain) fatty acids. Although this transport function of CD36 had already been discovered in adipocytes in the early nineties [3], and immediately thereafter in heart and muscle [4], the molecular mechanism by which CD36 facilitates the transport of fatty acids across the cell membrane is only beginning to be unraveled. The topography of CD36 is not compatible with its functioning as a membrane pore for fatty acids. Therefore, CD36 does not act as a true membrane 'transporter' (such as, for instance, GLUT proteins act as transporter of glucose across the membrane), but facilitates the transmembrane transport of fatty acids [5]. Nevertheless, for convenience, CD36 is commonly referred to as 'fatty acid transporter'.

Insight into the structure and functioning of CD36 was recently obtained from the crystal structure of its family member SR-B3/LIMP-2 [6] and further elaborated by Pepino and co-workers [7]. CD36 has two membrane spanning regions surrounding a large extracellular loop that contains a large hydrophobic cavity traversing the entire length of the molecule (Fig. 1). This cavity is considered to serve as a tunnel through which hydrophobic ligands (including cholesterol(esters) and fatty acids) are delivered from the extracellular space to the outer leaflet of the plasma membrane. More recent studies on the CD36 homologue in

Abbreviations: SR, scavenger receptor; SSO, sulfo-*N*-succinimidyl oleate; AMPK, AMP-activated kinase; SHR, spontaneously hypertensive rats; O-GlcNAc, O-linked *N*-acetylglucosamine; PKA, protein kinase A; PKC, protein kinase C; PAT, palmitoyl-transferase; PPT, palmitoyl-protein thioesterase.

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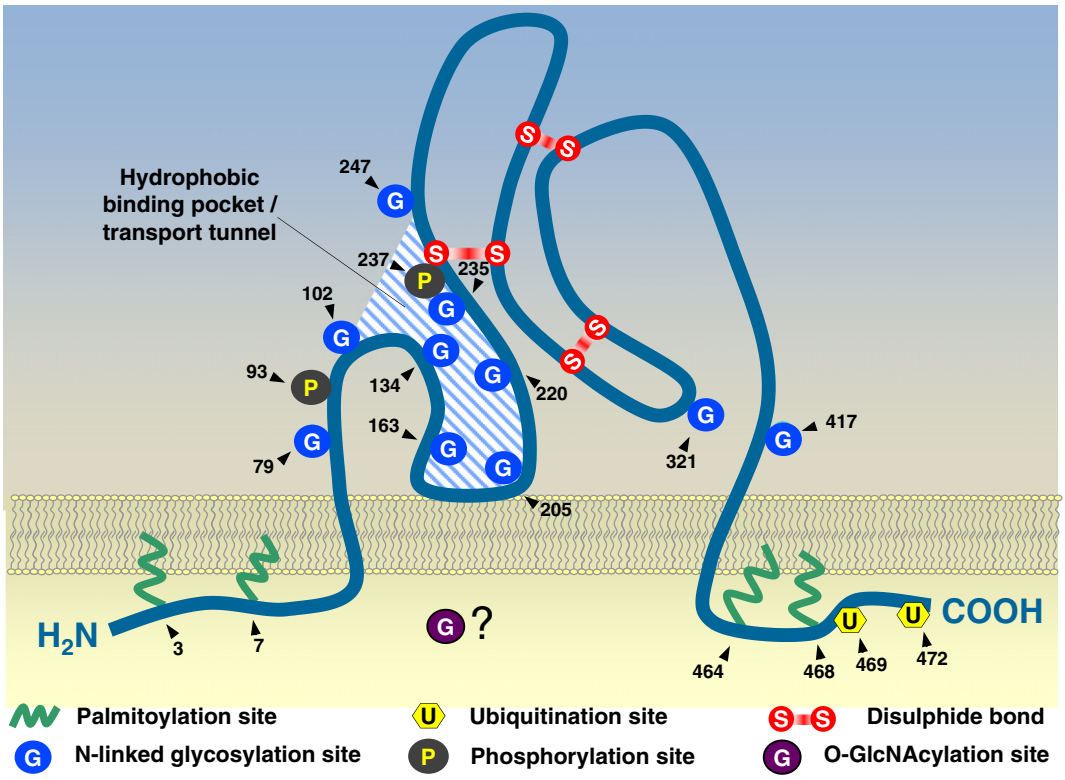

Fig. 1. Schematic presentation of the putative CD36 topology and known post-translational modifications. CD36 (SR-B2) has two transmembrane domains, with the small cytoplasmic tails being palmitoylated. The COOH terminus also has two ubiquitination sites. The large extracellular loop contains 10 *N*-linked glycosylation sites and two phosphorylation sites. The localization of the O-GlcNAcylation site is not yet known. Disulfide bonds between the extracellular cysteines are shown. The shaded area designates a hydrophobic pocket that is involved in ligand binding and serves as a tunnel through which ligands are delivered from the extracellular space to the external leaflet of the phospholipid bilayer of the membrane. Predictions of the three-dimensional structure of CD36 have been presented by others [6–8]. Arrowheads and numbers indicate the approximate amino acid residues. Modified from ref. [5], with permission.

Drosophila further confirm this concept [8]. With respect to fatty acid uptake, lysine residues bordering this pocket may interact with fatty acids through electrostatic interactions with the fatty acid-carboxylic group [9]. After entering the phospholipid bilayer of the membrane and translocation to the inner leaflet, presumably by a 'flip-flop' mechanism [10], desorption of the fatty acids into the intracellular compartment is facilitated by cytoplasmic fatty acid-binding protein (FABP) [5].

The first evidence for a major contribution of CD36 to bulk fatty acid uptake in muscles came from studies using the nucleophilic long-chain fatty acid derivative sulfo-*N*-succinimidyl oleate (SSO) [11,12]. SSO covalently binds to CD36 via Lys164 in the hydrophobic cavity thereby impairing CD36-mediated fatty acid uptake [9]. This SSO–CD36 binding at the cell surface appears to be specific, as other putative plasmalemmal fatty acid transporters (e.g., plasma membrane-fatty acid binding protein and members of the fatty acid transport protein family) are not labeled by this compound [9,13]. On the other hand, it was reported that in macrophages, SSO may also exert inhibitory effects on intracellular lipid metabolism independently of CD36 [14]. Conclusive evidence was obtained in studies with CD36-null mice, which also revealed the quantitative importance of CD36 for fatty acid utilization by mammalian tissues. These experiments showed that >40% and >70% of fatty acid uptake is mediated by CD36 in oxidative muscle [15] and heart [16], respectively. Recently, using an inducible and cardiomyocyte-specific CD36-null mouse model, the relevance of CD36 specifically for cardiac long-chain fatty acid uptake has been confirmed [17].

The role of CD36 in myocellular fatty acid utilization goes further than only serving as a facilitative transporter whereby the rate of transmembrane fatty acid transport is dependent solely on its presence in the membrane and the fatty acid gradient between the extracellular milieu and the myocellular cytoplasm. Thus, it has been well-established that within the overall processes of fatty acid uptake and subsequent metabolism, CD36 presents the major rate-controlling site, making it possible for myocytes to maintain low intracellular fatty acid levels even at physiologically high extracellular fatty acid concentrations [11]. The underlying molecular mechanism is based on the finding that CD36 is present not only at the cell surface, where it exerts its transport function, but also in intracellular storage sites, identified as endosomes. CD36 can migrate between both locations by means of vesicular transport along exocytotic and endocytotic pathways. A net translocation of CD36 to the sarcolemma is induced by several physiological stimuli, most notably, elevated circulating insulin levels and an increase in contractile activity whereupon, as a consequence, myocellular fatty acid uptake is increased. Insulin-induced CD36 translocation requires activation of the phosphatidylinositol-3-kinase–Akt2 signaling axis, and contraction-induced CD36 translocation is dependent on activation of AMP-activated kinase (AMPK) [5].

Various post-translational modifications have been reported to impact on CD36 and CD36 functioning and, in specific cases, have been related to malfunctioning of CD36 in disease. These modifications include glycosylation, acetylation, phosphorylation, palmitoylation, and ubiquitination. For each of these modifications, we will discuss alongside the existing literature the possible consequences for the regulation of fatty acid uptake in heart and muscle and, when data is available, specifically on the regulation of intracellular CD36 translocation.

2. Glycosylation of CD36

CD36 has a predicted molecular mass of 53 kDa, but in rodent muscle and heart the actual mass of this protein amounts to 88 kDa [3]. The difference is due mainly to extensive glycosylation. Rat CD36 has 10 potential glycosylation sites, and 8 of these are conserved between rat

and human [3]. Moreover, all of these predicted sites are located within the extracellular loop and indeed were observed to be glycosylated (Fig. 1). Classical *N*-linked glycosylation at asparagine residues occurs within the endoplasmic reticulum and the Golgi, and leads to the stable coupling of complex oligosaccharide structures to proteins. Glycosylation is common to many extracellular and secretory proteins, and is critical for correct folding, stability, transport to the cell surface, and function of proteins [18]. Glycosylation of CD36 is necessary for proper folding and trafficking to the plasma membrane [19]. Yet there is redundancy, as partially glycosylated CD36 mutants have been identified that also were properly distributed to the cell surface [19]. Remarkably, the exact glycosylation pattern did not matter in this respect. However, these glycosylation site mutants suffered from low expression levels. Furthermore, ligand recognition was not affected by alterations in the glycosylation pattern, as established for binding of CD36 to modified low-density lipoprotein [19]. With respect to the dynamic regulation of CD36 glycosylation, the gastrointestinal-derived hormone glucagon-like peptide-2 has been reported to increase the glycosylation of CD36 with an accompanying increase in the luminal absorption of fatty acids within hours [20]. However, the mechanism by which CD36 glycosylation leads to increased fatty acid absorption is not known. Hence, whether the fatty acid transport function of CD36 itself is altered by differences in glycosylation, is not known.

In spontaneously hypertensive rats (SHR), CD36 is mutated at multiple sites, the mutations of which have been proposed to be responsible for the reduced cardiac fatty acid uptake seen in this model [21]. One of these mutations relates to Asp102, the only potential *N*-glycosylation site mutated in SHR. Given that this site is located within the fatty acid binding pocket and, therefore, possibly important for the fatty acid transport function, mutation of this site may explain the decrease in fatty acid uptake upon pressure overload in this rat model. On the other hand, total CD36 protein expression in SHR rats is greatly reduced, perhaps due to mutation at the Asp102 residue or at one of the other mutated sites, resulting in a decrease in its stability [21]. Hence, further studies need to be undertaken to study the role of glycosylation in altered fatty acid uptake in SHR.

In contrast to classical glycosylation, the modification of proteins by O-linked *N*-acetylglucosamine (O-GlcNAc) is a dynamic process occurring in the cytoplasm and involving a reversible binding of a single O-GlcNAc moiety to serine/threonine residues [22]. The process requires two enzymatic activities to attach and to remove the O-GlcNAc moiety, respectively. The attachment is mediated by O-GlcNAc transferase (OGT), and driven by the intracellular availability of O-GlcNAc formed in the hexosamine biosynthesis pathway. CD36 has been proposed as a target for O-GlcNAcylation [23]. Namely, glucosamine addition to perfused hearts increases both OGT binding to CD36, abundance of CD36 at the sarcolemma, and fatty acid oxidation, leading the authors to conclude that O-GlcNAcylation of CD36 induces CD36 translocation to the sarcolemma and subsequently enhances myocellular fatty acid uptake [23].

3. Acetylation of CD36

Proteomic analysis of lysine acetylation sites in mouse and rat tissues revealed acetylation of CD36 at lysines 52, 166, 231, and 403 [24]. Acetylation of these sites was confirmed by mass spectrometry analysis of human CD36 [9], indicating that these acetylation sites are conserved from rat to man. However, the dynamics and functional consequences of these acetylations for CD36 expression and/or functioning have not yet been investigated.

4. Phosphorylation of CD36

CD36 has at least two consensus phosphorylation sites, i.e., at Thr92 and Ser237, both of which are within the extracellular loop (Fig. 1). The first site is a putative protein kinase C (PKC) site, and the second site is recognized by protein kinase A (PKA) [25,26]. In resting platelets, the Thr92 site is constitutively phosphorylated resulting in diminished thrombospondin binding under non-stimulated conditions [25]. This phosphorylation occurs in the Golgi on newly synthesized protein and is retained upon trafficking of CD36 to the cell surface and subsequent extracellular exposure of this site [27]. The other site is subject to regulation by an ecto-kinase pathway involving PKA. In platelets, CD36 ecto-phosphorylation inhibits fatty acid uptake in a reversible manner [28]. Yet, this pathway may not be operative in heart and muscle, as activation of PKA by isoproterenol, dibutyryl-cAMP or the phosphodiesterase inhibitor amrinone did not influence fatty acid uptake into cardiomyocytes [29]. Hence, in heart and muscle, CD36 phosphorylation may be of only minor importance. Perhaps, the ecto-kinase responsible for the inhibitory phosphorylation in platelets is not present in the interstitial space in heart and muscle.

The CD36 phosphorylation status also appears regulated by phosphatases. In mouse small intestinal enterocytes, CD36 is co-localized with global intestinal alkaline phosphatase, and de-phosphorylation by this phosphatase resulted in increased fatty acid uptake [30]. These data are in line with the observations in platelets that CD36 phosphorylation is inhibitory for fatty acid uptake.

It is noteworthy to mention that phosphorylation processes are definitely linked to CD36 functioning and regulation of fatty acid utilization in heart and muscle. First of all, phosphorylation of AMPK is critically involved in vesicle-mediated CD36 translocation from endosomes to the sarcolemma and contraction-stimulated fatty acid uptake [5]. Moreover, phosphorylation of Akt and AS160 are necessary for insulin-stimulated CD36 translocation and increased fatty acid uptake [31,32]. Finally, CD36 is also known as a signaling hub upon binding to fatty acids. This leads to phosphorylation of Src-protein-tyrosine kinases, particularly of Fyn and Yes and subsequent activation of calcium signaling in gustatory cells [33]. In muscle, fatty acid-induced CD36-mediated Fyn phosphorylation leads to AMPK activation, feeding forward to increased fatty acid oxidation [34]. However, these mechanisms are outside the scope of this review.

5. Ubiquitination of CD36

Ubiquitination of proteins is the coupling of proteins to ubiquitin (a small protein of 8.5 kDa). Protein ubiquitination is generally considered to trigger the degradation of these proteins through directing them to proteasomes [35]. In short, there are three main steps in ubiquitination: activation, conjugation, and ligation, executed by ubiquitin-activating enzymes (E1), ubiquitin-conjugating enzymes (E2), and ubiquitin ligases (E3), respectively. Substrate specificity is governed by E3, of which there is a great variety. More recent investigations reveal that several types of protein ubiquitination appear to exist, and the different types have different impacts on their substrates. The classical pathway targeting proteins for proteasomal degradation is the poly-ubiquitination pathway linked to Lys48 on ubiquitin. On the other hand, poly-ubiquitination linked to Lys63 on ubiquitin as well as mono-ubiquitination are considered as non-degradative, and serve other purposes, such as protein complex formation [36,37].

The first evidence that CD36 is a substrate for ubiquitination came from studies in cell lines, including C2C12 myotubes [38]. CD36 appears to be constitutively poly-ubiquitinated involving both Lys48 and Lys63 linkage (Fig. 1). The degree of poly-ubiquitination was differentially affected by exposure of cells to fatty acids or insulin: fatty acids increase whereas insulin decreases the poly-ubiquitination of CD36. Concomitantly, fatty acids reduce CD36 protein levels and decrease cellular fatty acid uptake, and insulin has opposite effects. The degree of poly-ubiquitination of CD36 did not affect the relative CD36 distribution between intracellular storage compartments and cell surface [38]. Site-directed mutagenesis revealed that one or two lysines of CD36 located within the small intracellular C-terminal segment, i.e., Lys469 and Lys472, are responsible for this CD36 regulation by poly-ubiquitination [38].

More recently, it was found that CD36 is a target of Parkin, an E3 ligase. The malfunctioning of this enzyme is causally related to the onset of Parkinson's disease [39]. Livers of mice on a high-fat diet displayed increased Parkin levels and increased CD36 levels as well as increased lipid accumulation and insulin resistance [40]. In Parkin-knockout mice, hepatic CD36 levels were markedly reduced and the maladaptive responses towards a high-fat diet concerning hepatic lipid levels and insulin signaling were completely blunted. Parkin appeared to mono-ubiquitinate CD36 leading to an increase in its stability [40]. It is expected that one of the intracellular C-terminal lysines within CD36 is targeted by Parkin. Moreover, this lysine residue could then be an integration point of the effects of fatty acids and Parkin on CD36 [41]. Yet, this Parkin-mediated mono-ubiquitination and stabilization of CD36 in liver seems to conflict with the fatty acid-mediated poly-ubiquitination and degradation of CD36 in cell lines. Namely, Parkin expression is induced by fatty acids [40], so it is to be expected that fatty acids should stabilize or increase the CD36 protein level rather than decreasing it. A way out of this paradox is provided by the fact that Parkin exhibits both mono- and poly-ubiquitination functions [42]. Hence, Parkin downstream effects can be proteasome-dependent as well as independent. Perhaps the function of Parkin varies between different tissues and/or circumstances, making it to operate as a mono-ubiquitinase in one tissue under a specific condition and as a poly-ubiquitinase in another tissue or in a different condition. Alternatively, CD36 could be targeted by different, yet unidentified E3 ligases in different tissues. Another controversial finding related to Parkin is that this E3 ligase does not appear to be responsible for the increased CD36 expression levels in the livers of aged mice on a high-fat diet, because Parkin levels were found to remain unaltered during ageing [43].

Finally, long-term incubation of HL1-cardiomyocytes or primary rat cardiomyocytes with insulin and/or long-chain fatty acids did not alter myocellular protein levels of CD36 [44,45], suggesting that CD36 ubiquitination does not occur in cardiomyocytes upon exposure to either one or both stimuli. The latter observations underscore the notion that the effects of E3 ligases on CD36 ubiquitination are strictly tissue-specific.

6. Palmitoylation of CD36

There are several types of modification of proteins by lipids, among which protein myristoylation (covalent attachment of a C14-fatty acid group) and protein palmitoylation (covalent attachment of a C16-fatty acid group) are most common [46,47]. In contrast to myristoylation, which is considered to be an irreversible protein modification, the palmitoyl moiety can be removed so that palmitoylation is compatible with short-term regulation. The reversible covalent bond occurs between palmitate and cysteine residues of proteins via a thioester linkage in most cases, and less frequently to serine and threonine residues of proteins [46,47]. In more detail, dynamic protein palmitoylation is an enzymatic process, which requires palmitoyl-transferases (PATs) and palmitoyl-protein thioesterases (PPTs) for palmitoylation and depalmitoylation, respectively. Regarding the function of protein palmitoylation, it is generally accepted that palmitoylation regulates the subcellular localization, membrane interactions, as well as subcellular trafficking of proteins [46,47]. Remarkably, palmitoylation has no obvious sequence requirements other than the cysteine residue, but palmitoylation sites are often found in the proximity of transmembrane segments.

The first reports that CD36 was palmitoylated came from studies in adipocytes, in which CD36 appeared to be one of the major palmitoylation targets, while this modification could be further increased by insulin [48]. Palmitoylation occurs on the two N-terminal and two C-terminal cysteines, in human CD36 corresponding to residues 3, 7, 464, and 468 [49]. Both cysteine pairs are intracellular and adjacent to the transmembrane segments (Fig. 1). Mutation of the two N-terminal cysteines into alanines and the two C-terminal cysteines into serines decreased the maturation of CD36 to the fully glycosylated form, which was accompanied by a decrease in stability [50]. Also, a CD36 mutant in which the four intracellular cysteines have been converted into serines showed incomplete processing and decreased expression [51]. Yet, this mutant, a C-terminal truncation mutant, or other CD36 mutants in which either one or two of the cysteines were replaced by serines, each showed proper localization at the cell surface in Chinese hamster ovary (CHO) cells or HEK293 cells [49,51]. On the other hand, all four intracellular cysteines were observed to be needed for translocation of CD36 upon insulin stimulation of CHO cells or stimulation by the AMPK activator AICAR. However, immunoprecipitation experiments showed that the 4*Cys→Ser-CD36 mutant was not differentially incorporated with [^{3}H]palmitate than wild-type CD36 in the absence or presence of insulin, excluding the role of palmitoylation and suggesting that another post-translational mechanism involving all four cysteines is required for CD36 translocation [51]. In conclusion, palmitoylation at its intracellular cysteines is necessary for CD36 maturation [50]. This palmitoylation could be mediated by Swf1, a member of the PAT family, which is resident to the endoplasmic reticulum and responsible for palmitoylation of many membrane proteins that are modified at cytoplasmic cysteine residues close to the transmembrane domain [52].

7. Conclusions and perspectives

CD36 undergoes various types of post-translational modifications in a tissue-, condition-, and time-dependent manner (Table 1). These modifications each have distinct consequences for CD36 functioning and, in addition, may show a specific interplay that together makes the regulation of the functioning of CD36—for instance, in regulating cellular fatty acid uptake—difficult to unravel. Phosphorylation may regulate the fatty acid transport function of CD36, whereas *N*-linked glycosylation, ubiquitination, and palmitoylation each affect CD36 expression and stability. In contrast, none of these modifications appear to alter CD36 membrane localization or function. The *N*-linked glycosylation and palmitoylation processes occur as part of CD36 maturation in the endoplasmic reticulum/Golgi and are therefore not likely to contribute to short-term regulation of fatty acid uptake in any tissue. Yet, CD36 ubiquitination by insulin occurs within a time frame of 30 min, giving this modification type the ability to impact on fatty acid uptake at the short-term level, as indeed has been shown [38].

CD36 translocation to the plasma membrane and subsequent internalization (i.e., intracellular recycling) is a main determinant of short-term regulation of myocellular fatty acid uptake by insulin or AMPK activators, but the mechanisms underlying CD36 translocation and internalization have been incompletely resolved. It is, however, clear that most of the of the post-translational modification types, i.e., glycosylation, phosphorylation, ubiquitination, and palmitoylation, impacting on CD36 are not important for insulin-stimulated or AMPK-mediated CD36 translocation. Only O-GlcNAcylation of CD36, as induced upon stimulation of the hexosamine biosynthesis pathway, has been shown to increase CD36 translocation, but this is independent of insulin or AMPK activation [23].

Taking this a step further, it is possible that in the insulin-resistant or diabetic heart, which shows elevated CD36 levels at the cell surface and an increased rate of fatty acid uptake [5], CD36 undergoes increased O-GlcNAcylation, and therefore increased translocation of CD36 to the cell surface. This increased CD36 translocation then sets the stage for further maladaptive lipid-induced alterations negatively impacting on contraction force of cardiomyocytes [53]. Such hypothetical sequence of events would be in line with earlier observations that there is increased flux through the hexosamine biosynthesis pathway in insulin-resistant muscle [23]. Moreover, in the diabetic heart, overall protein O-GlcNAcylation has been increased and this may be responsible for the adverse effects of diabetes on cardiac function [54]. Another mechanism by which CD36 function is upregulated in diabetic tissues and possibly contributes to high-fat diet-induced insulin resistance, is displayed by

Table 1
Reported effects of the various post-translational modifications of CD36 on its expression and functioning in cellular fatty acid uptake.

Post-translational modification type	Tissue or cell type studied	CD36-related parameters and cellular fatty acid uptake			
		CD36 expression	CD36 intrinsic fatty acid transport activity	CD36 translocation to the plasma membrane	Fatty acid uptake
N-linked glycosylation	Various tissues and cell types	↑	n.k.	–	↑
O-GlcNAcylation	Heart	–	–	↑	↑
Acetylation	Various tissues	n.k.	n.k.	n.k.	n.k.
Phosphorylation	Platelets, enterocytes	n.k.	↓	–	↓
Poly-ubiquitination	Muscle, adipose tissue	↓	–	–	↓
Mono-ubiquitination	Liver	↑	–	–	↑
Palmitoylation	Adipocytes, CHO cells	↑	–	–	↑

Explanation of symbols: ↑, positive (stimulatory) effect; ↓, negative (inhibitory) effect; –, no effect; n.k., effect not known. Note that the implications of these post-translational modifications were studied mostly in a particular tissue or cell model, so that extrapolation to other tissues or cell models may not apply. See text for more detailed explanation and literature references.

the intestine. High-fat diet supplemented to rodents simultaneously upregulates CD36 and global intestinal alkaline phosphatase in enterocytes, thereby increasing CD36-dependent fatty acid uptake [30]. Whether increased alkaline phosphatase action contributes to increased cardiac fatty acid fluxes in the diabetic heart is not known. Besides these examples of post-translational CD36 modifications increasing fatty acid uptake, it should be investigated whether other post-translational modifications of CD36 also occur in the insulin-resistant/diabetic heart or in any other cardiac metabolic disorder. For instance, increased CD36 stabilization due to palmitoylation or to alterations in ubiquitination could also lead to excessively increased fatty acid fluxes into the heart and subsequent impairments in insulin signaling and contractile function. Finally, other post-translational modifications, such as methylation, isoprenylation, and sumoylation, might occur and could impact on CD36 but, to our knowledge, these have not yet been investigated. Therefore, these additional modification types could be a topic for future studies.

Conflict of Interest

Please note that the authors have no conflict of interest.

Transparency document

The Transparency document associated with this article can be found, in the online version.

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